THE SCOPE OF PHENOL-CHLOROFORM-ACETONITRILE AS A SOLVENT SYSTEM IN NONAQUEOUS TITRIMETRY

By L. G. Chatten

From the Pharmaceutical Chemistry Section, Food and Drug Directorate, Ottawa, Canada

Received June 17, 1955

Glacial acetic acid has been considered by many workers[1–5] to be the solvent of choice for the nonaqueous titration of salts of organic bases. Markunas and Riddick[1] reported representative groups of over 400 compounds which they tested, while Pifer and Wollish[2] published a report which mainly dealt with the determination of halide salts of organic bases, using glacial acetic acid as the solvent.

Recently a method was devised in this laboratory[6] which facilitated the quantitative determination of codeine phosphate when combined with acetylsalicylic acid, phenacetin and caffeine, by using a phenol-chloroform-acetonitrile solvent system. From the results obtained during that investigation, it was believed this solvent system may be used to determine the salts of other organic bases.

Experimental

Reagents. (*a*) Perchloric acid 70–72 per cent.; (*b*) dioxane, Eastman white label; (*c*) glacial acetic acid, A.C.S. grade; (*d*) phenol, reagent grade; (*e*) chloroform, A.C.S. grade; (*f*) acetonitrile, repurified by shaking with amberlite IRC-50 as previously reported by this laboratory[7]; (*g*) 0·05N acetous perchloric acid standardised against potassium acid phthalate, A.C.S. grade; (*h*) 0·05N perchloric acid in dioxane, standardised as above; (*i*) methyl red 0·25 per cent. in 2 g. of phenol and 100 ml. of chloroform.

Apparatus. A Fisher titrimeter, complete with glass-calomel electrode combination and semimicro burette.

Procedure. A sample of the organic salt, sufficient to permit a titration of 2 to 3 ml., was weighed into beaker, 5 g. of phenol and 10 to 20 ml. of chloroform were added. The mixture was stirred electromagnetically to complete solution, then 50 ml. of acetonitrile and 1 to 2 drops of methyl red indicator were added. As the end-point is approached, the indicator passes through several stages of colour from peach to red-violet. The final change is usually very sharp. In the potentiometric titrations, millivolt readings were recorded for every 0·02 ml. of titrant in the vicinity of the end-point, which was taken at the millivolt reading where the ratio dE/dV was a maximum.

Experimental Results and Discussion

The results obtained when aliquots of pure salts of amines and heterocyclic nitrogen compounds, dissolved in phenol-chloroform-acetonitrile solvent system and titrated with 0·05N perchloric acid in dioxane, are recorded in Table I. Water content of the compounds was determined

TABLE I

TITRATION OF PURE SALTS

Salt	Potentiometric		Visual		Per cent. water (Karl Fischer)
	Mg. taken	Mg. recovered	Mg. taken	Mg. recovered	
Amphetamine sulphate	52·0	52·5	52·0	52·5	
	50·6	50·4	36·0	36·0	0
	42·0	42·3	36·9	36·6	
Dexamphetamine sulphate	54·4	54·3	42·1	42·3	
	44·9	44·5	38·8	38·7	0
	45·3	44·8	54·4	54·3	
Ephedrine sulphate ..	43·6	43·4	45·7	45·4	
	42·4	42·4	45·0	44·6	0
	41·7	41·9	45·3	45·0	
Morphine sulphate ..	88·6	87·4	88·6	87·4	
	84·8	83·8	89·1	89·6	9·03
	87·6	87·0	84·8	83·8	
Codeine sulphate ..	83·3	84·3	77·5	76·9	
	70·9	71·9	35·5	36·0	6·39
			70·9	71·9	
Butacaine sulphate ..	37·4	37·4			
	77·8	77·4	Indicator	unsuitable	—
	76·0	75·9			
Quinine sulphate ..	63·4	63·6			
	66·8	67·0	Indicator	unsuitable	4·3
	66·9	67·1			
Cinchonine sulphate ..	26·2	25·9			
	27·1	26·6	Indicator	unsuitable	2·77
	27·7	27·8			
Cinchonidine sulphate	25·7	25·5			
	29·7	28·9	Indicator	unsuitable	3·89
	25·3	24·7			
Strychnine sulphate ..	93·7	93·7	79·0	78·5	
	83·9	83·5	93·7	93·7	10·5
	87·6	87·1	87·6	87·1	
Physostigmine sulphate	66·3	66·5	66·3	66·5	
	74·2	74·7	66·9	67·2	2·3
	65·3	65·0	68·1	68·4	
Physostigmine salicylate	52·0	51·1	52·0	51·7	
	50·1	49·7	50·1	50·1	0·4
	50·8	50·3	50·8	50·7	
Phenindamine tartrate	45·3	44·6	45·6	44·6	
	55·8	54·6	45·3	44·6	
	50·9	49·8	55·8	54·6	
Pilocarpine nitrate ..	30·3	30·3			
	36·7	36·9	Indicator	unsuitable	—
	34·6	36·1			
Codeine phosphate ..	Previously reported[6]		43·4	43·6	
			46·2	46·6	5·26
			44·3	44·6	
Morphine acetate ..	46·8	45·7	48·0	46·9	
	53·5	51·9	53·5	52·3	9·6
	49·2	47·6	46·8	45·7	
Dihydrocodeinone bitartrate	57·1	58·1	64·3	64·6	
	56·4	56·8	66·3	65·8	8·35
	65·6	65·6	65·6	66·0	
Dioxyline phosphate..	41·9	41·7	43·3	43·6	
	62·7	62·8	41·9	41·1	2·14
	58·6	58·1	58·6	58·1	

by Karl Fischer titrations and adjustments were made in the molecular weights where necessary. Where a change in molecular weight occurred due to the water content, the new molecular weight was employed to calculate the recovery of the drug. Comparative assays were made with glacial acetic acid as a solvent and 0·05N acetous perchloric acid as titrant. Thus, it was found that neither potentiometric nor visual titrations with crystal violet could be performed for butacaine sulphate, physostigmine sulphate and physostigmine salicylate in the latter system whereas excellent potentiometric changes occurred for all three salts in phenol-chloroform-acetonitrile and very sharp visual end-points were noted for the two physostigmine salts. With the exception of the sulphates of cinchonine and cinchonidine, markedly improved potentiometric end-points occurred for all salts in Table I. Where methyl red could be used, the indicator change was, in almost every instance, much sharper than that obtained for the same salt using crystal violet in glacial acetic acid.

Riddick[8,9] reported that there was considerable evidence that mixed solvents may be superior to a single solvent in general solvent power and in sharpness of the colour change of indicators or in the potentiometric break. Pifer and Wollish[2] found that the addition of dioxane to glacial acetic acid enhanced the potentiometric break, while Fritz and Fulda[10] demonstrated the advantages of a mixed solvent system in their work on the titration of certain weak bases.

A comparison of the potentiometric curves obtained for ephedrine sulphate, in the two respective solvent systems, is given in Figures 1 and 2.

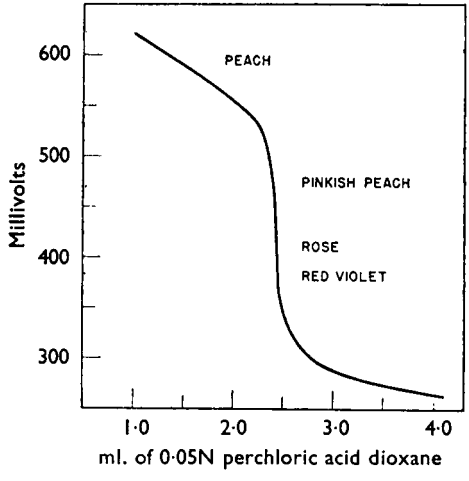

FIG. 1. Titration of ephedrine sulphate in phenol–chloroform–acetonitrile solvent system.

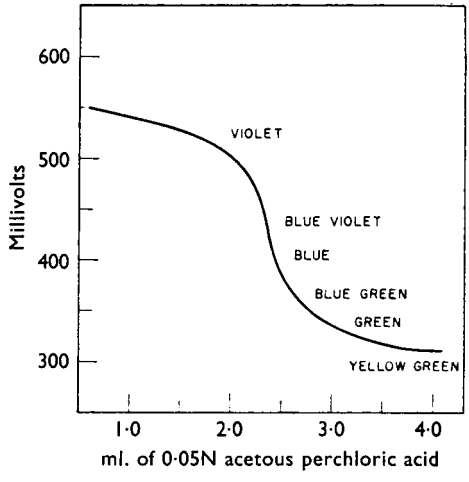

FIG. 2. Titration of ephedrine sulphate in glacial acetic acid.

It is seen that the change in potential at the end-point, in phenol-chloroform-acetonitrile, is considerably larger than that obtained for the same compound in glacial acetic acid. In fact, the dE/dV for ephedrine sulphate, in the former solvent system, ranges from 2500 to 3000, whereas

the dE/dV for the same drug in the latter system is only 500 to 600. In addition, it was noted that the dE/dV for all salts in Table I, with the exception of the cinchona alkaloidal sulphates and pilocarpine nitrate were equal to or greater than 2000 in the phenol-chloroform-acetonitrile solvent system whereas, in glacial acetic acid, only the dE/dV of pheninamine tartrate and of dioxyline phosphate exceeded 800. For most of the other compounds it was much less.

Saunders and Srivastava[11] utilised an aqueous-alcoholic solvent system to titrate a number of salts of organic bases. Although they make no mention of the dE/dV at the end-points, it would seem from the appearance of their curves that generally they were considerably smaller than those obtained in phenol-chloroform-acetonitrile and in no instance have they been able to perform a visual titration.

Gautier and Pellerin[12], in reporting the assay of sulphates of organic bases, found it was essential to precipitate the sulphate by the addition of benzidine. Higuchi and Concha[13] pointed out that considerable difficulty was encountered in the titration of sulphates because of their low solubility in glacial acetic acid. While not all salts of organic bases are soluble in phenol-chloroform, those reported in Table I possess a high solubility in that system. Although amphetamine and dexamphetamine sulphates are readily soluble in phenol-chloroform, the addition of acetonitrile turned the solution milky. This phenomenon had no effect upon the quantitative recoveries as the solution cleared during the titration before the end-point was reached. The phenol-chloroform combination possess the solubilising properties but acetonitrile must be added for its stabilising effect in potentiometric titrations[6]. In fact, methyl red will not function as an indicator if phenol-chloroform is used alone but requires the presence of acetonitrile.

However, phenol-chloroform-acetonitrile possesses certain limitations as a solvent system. The solubilities of morphine tartrate, morphine meconate, chlorothen citrate, the sodium barbiturates as well as the alkali-metal salts of carboxylic acids and of the antibiotics were so small as to render the system valueless for them. Each compound should be tested individually before a decision about its solubility can be reached.

Halogen salts cannot be titrated as a side reaction occurs with the solvent system when mercuric acetate is dissolved in it. In addition, for reasons unexplained, no visual or potentiometric end-point could be detected for pyrilamine maleate and the recovery of doxylamine succinate was not quantitative.

SUMMARY

1. Phenol-chloroform-acetonitrile, as a nonaqueous solvent system, has been applied to a number of salts of organic bases and found to offer the advantages of increased solubility and increased ease of detection of end-points.

This finding appears to agree with the results of other workers who have employed mixed solvents in nonaqueous titrimetry.

REFERENCES

1. Markunas and Riddick, *Analyt. Chem.*, 1951, **23**, 237.
2. Pifer and Wollish, *ibid.*, 1952, **24**, 300.
3. Gautier and Pellerin, *Ann. pharm. franç.*, 1952, **10**, 401.
4. van Arkel, *ibid.*, 1952, **10**, 636.
5. Pifer, Wollish and Schmall, *J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 509.
6. Pernarowski, Chatten and Levi, *ibid.*, 1954, **43**, 746.
7. Levi, Chatten and Pernarowski, *ibid.*, 1955, **44**, 61.
8. Riddick, *Analyt. Chem.*, 1952, **24**, 41.
9. Riddick, *ibid.*, 1954, **26**, 77.
10. Fritz and Fulda, *ibid.*, 1953, **25**, 1837.
11. Saunders and Srivastava, *J. Pharm. Pharmacol.*, 1951, **3**, 78.
12. Gautier and Pellerin, *Ann. pharm. franç.*, 1954, **12**, 505.
13. Higuchi and Concha, *J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 173.